

REMARKS/ARGUMENTS

Reconsideration of this patent application is respectfully requested in view of the following remarks.

Regarding the restriction requirement which was maintained by the Patent Examiner, it is reasonable to assume that the restriction to "TEMPO analogs" does not mean that there is a limitation to the seven compounds originally proposed by the Patent Examiner in group 1. Instead, this term relates to the group of nitroxyl compounds represented by the introduction of the general formula I into claims 1 and 11 which clearly also represent "TEMPO analogs".

It is respectfully pointed out that the subject-matter of the claims is not directed to the use, per se, of the nitroxyl compounds. These compounds are part of the reaction mixture for catalytic purposes, but the effect of such catalysts is independent from its specific structure. The presence of the nitroxyl compounds is necessary to obtain conversion (therefore they are part of the claim), but a successful conversion is independent from the exact structure of the nitroxyl compounds. Furthermore the nature of the nitroxyl compounds is not a distinctive feature.

The subject-matter of the pending claims is directed to the

oxidation of alkynic alcohols. Therefore the subject-matter of the claims is strictly limited to the oxidation of such starting material under defined reaction conditions (distinctive features). For search purposes, a person skilled in the art would use such distinctive features upon which to base his search. It is respectfully submitted that there is no need to restrict the search by restricting the catalytic auxiliary material (nitroxyl compounds).

The objection of the Patent Examiner relating to the scope of the claims for N-oxyl compounds (claim 1 and 11) is respectfully believed to be in error for several reasons. The Patent Examiner states that compounds according to formula (I) in Zedda et al. (US 2004/0063932, claim 1) would be encompassed by the present claims. This is respectfully believed to be in error. This is due to the Applicants' proposed restriction, any piperidine derivatives substituted with such a nitrogen atom in 4 position are no longer any part of the claims. Hence, any argumentation based on formula (I) (Zedda et al., US 2004/0063932) is irrelevant for the pending claims.

And even if formula (I) (Zedda et al., US 2004/0063932) would be encompassed by the original wording of the claims ("nitroxyl compounds"), this could never be a reason for a restriction requirement. This is because Zedda et al. has

already stated that a compound according to formula (1) is "particularly useful as catalyst for the selective oxidation of alcohols to 'carboxylic acids'" as an equivalent for TEMPO (Zedda et al., US 2004/0063932. [0001] and Example E).

But Zedda et al. did not disclose the use of such a catalyst for the specific oxidation reaction which is the subject matter of the pending claims.

Furthermore, the objection of the Patent Examiner is not justified because similar claims for nitroxyl compounds as a catalytic oxidant were already accepted by the USPTO, for example in Merbouh et al. (US 6,498,269. claim 1 and claims 7-11) - also quoted in the Office Action in another context. Based on the Patent Examiner's argumentation, such claims should have been unsearchable.

For all these reasons, it is respectfully requested that the Requirement for Restriction be withdrawn.

The Applicants comment upon the prior art rejections of the claims as follows.

It is respectfully pointed out that there are three

essential and new features in claim 1 in view of *Li et al.*: (1) the pH value, (2) the nature of the stoichiometric oxidant, and (3) the fact of using a continuous process.

Li et al. disclose that the TEMPO-catalyzed oxidation of primary alcohols using stoichiometric amounts of bleach (NaOCl) under alkaline conditions (which is not the subject matter of the process disclosed in *Li et al.*) Instead, this is the citation of the classic reaction protocol by Anelli et al. for comparison purposes; col. 1, lines 25-26) resulted in poor yield and purity of the desired products (col. 6, lines 44-67; col. 7, Table 1, right column ("Yield (NaOCl)"). The "classic" Anelli protocol was only used for comparison purposes in Table 1. Compound 2h was only obtained in less than 20 % yield using the Anelli protocol (cf. also the identical publication of *Li et al.* in *J. Org. Chem.* 1999, 64, 2564, Table 1, right column ("Yield (NaOCl)").

The problem to be solved at *Li et al.* was to provide a process which avoids unwanted chlorinated by-products (col. 1, lines 50-52; col. 5-6, lines 14 ff). The problem was solved by using stoichiometric NaClO₂ (sodium chlorite) and catalytic NaOCl (sodium hypochlorite) and catalytic TEMPO (col. 1, lines 44-47; col. 7, Table 1, column "Yield (NaClO₂)"). *Li et al.* further disclose that "the TEMPO/NaClO ratio should be >2 to reduce the chances of chlorination" (col. 6, lines 24-25). *Li et al.*.

disclose that "the reaction was faster at lower pH" (col. 6, line 19) and therefore lower pH was more advantageous for such process.

Li et al. stated explicitly that the procedure using stoichiometric NaClO₂ (sodium chlorite) and catalytic NaOCl (sodium hypochlorite) and catalytic TEMPO is superior to the protocol with stoichiometric NaOCl and catalytic TEMPO which resulted in poor yield and purity for Li's purposes (col. 6, line 46 and col. 9, line 29-41).

Additionally, having a large scale industrial process in mind, "it should be noted, that mixing of bleach and NaClO₂" is dangerous "since some toxic and potentially explosive chlorine dioxide (ClO₂) may be generated" (col. 6, line 29-32). The process of the present invention is superior to the one described by Li et al. from a technical point of view, as no explosive and toxic gases will occur.

Li et al. did not disclose the use of "a pH greater than 7" (alkaline conditions) for the classic NaClO protocol using stoichiometric amounts of NaOCl (sodium hypochlorite) as an oxidant (Annelli et al.).

The disclosure of Li et al. is opposite to the subject matter of the present invention. In view of Li et al., a person skilled in the art would not try to oxidize primary alcohols with stoichiometric sodium hypochlorite (NaOCl). And a person skilled in the art would not utilize (higher pH) alkaline reaction conditions as Li et al. teaches that lower pH is more advantageous.

Furthermore Li et al. does not disclose the advantage of continuously adding alkyne alcohol and hypohalite to the reaction mixture. This is an essential feature which will overcome the already cited problems of the prior art classic Anelli protocol.

Therefore, the present invention is not obvious in view of Li et al. The deficiencies in the teachings of the primary reference to Li are not overcome by the disclosures of the secondary references to Azerbaev or Merbouh.

With respect to Azerbaev et al., the Patent Examiner has interpreted Azerbaev et al. incorrectly. Azerbaev et al. describes numerous reactions of alkynes which have nothing in common with the compounds and reactions of the present invention.

The subject-matter of Azerbaev's disclosure is not the oxidation of alkyne alcohols ($-C\equiv C-CH_2-OH$) but instead is

- (i) the oxidation of terminal alkynes ($-C\equiv C-H$)
- (ii) via halogenation using KOBr resulting in $-C\equiv CBr$ (this is exactly what the present process wants to avoid).
- (iii) followed by hydrogenation resulting in $-CH_2-CH_2-Br$ / $-C(O)-CH_2-Br$ or
- (iv) a Grignard-type reaction using Mg/CO₂ resulting in $C\equiv C-COOH$ followed by hydrogenation and other subsequent reactions.

Thus, Azerbaev et al. do not disclose any kind of oxidation of alkyne alcohols to carboxylic acids.

Furthermore, the Patent Examiner argued incorrectly that Azerbaev et al. "taught that KOH would favour the transformation of intermediary compounds into the alkynyl carboxylic acid product". De facto Azerbaev et al. discloses a reaction using KOH as a reagent: $HOCMe_2C\equiv C-COOH$ is converted in the presence of KOH to result in $HC\equiv C-COOH$. However, Azerbaev's et al. starting material contained already the alkynecarboxylic acid functionality which was not transformed by KOH. The disclosed reaction takes place at the backbone of the molecule and is irrelevant for the process of the present invention.

Therefore, Azerbaev et al. did not disclose a single hint for the preparing of alkynecarboxylic acids by continuous

oxidation of alkyne alcohols under basic conditions, since they disclose a totally different chemistry.

With respect to the obviousness of the present invention, it is necessary to properly assess the prior art.

The use of hypochlorite as stoichiometric oxidant under basic reaction conditions (bleaching liquor) is already known from Anelli et al. It is further known in the art, that unsaturated alcohols are considered to be unsuitable for such oxidation processes (cf. Specification pages 4 to 5 and cited references therein). The already cited comparison examples of Li et al. (compound 2h in Table 1, right column) also teach and confirm the unsuitability of the Anelli process for such substrates. Therefore Li et al. proposed an alternative process using a different oxidant (chlorites).

The problem to be solved by the present invention was to provide a process for the preparation of alkyne carboxylic acids starting from alkyne alcohols using the large scale available bleaching liquor (lower cost, less toxic and less dangerous) but avoiding unwanted side-reactions.

It was surprisingly found that by continuously adding the alkyne alcohol and the hypohalite the problems of the prior art can be solved.

The Patent Examiner states that it is obvious to "operat[e] a known process continuously". However, in the prior art the oxidation process of alcohols with NaOCl and in the presence of TEMPO was described discontinuously and proved to be unsuitable or very low yielding for the oxidation of unsaturated alcohols (P.L. Anelli, O. Biffi, F. Montanan, S. Quici, J.Org.Chem. 1987, 52, 2559; Li et al., col. 6, lines 44-67, col. 7, Table 1, right column "Yield (NaOCl)").

The present invention claims a process for preparing alkyne carboxylic acids characterized by the oxidation of an alkyne alcohol with stoichiometric hypohalite in the presence of a N-oxyl compound at a pH of higher than 7 with continual addition of the alkyne alcohol and of the hypohalite to the reaction mixture. The corresponding alkyne carboxylic acids were obtained in high yields (cf. comparison example and examples within the Specification).

A person skilled in the art would not have expected this improvement by replacing a discontinuous process by a continuous

process. This result was surprising and unexpected and therefore this difference is patentable.

Li et al. discloses different reaction conditions and cites *Anelli et al.* for comparison purposes only.

Neither *Li et al.* nor any other cited prior art gives any hint to the person skilled in the art how to overcome these prior art problems with the classic bleaching liquor in connection with the oxidation of unsaturated alcohols as substrates.

Therefore the teaching of *Li et al.* and the other cited prior art is irrelevant for the assessment of the obviousness of the present invention.

With respect to point 3 of the Office Action, it is to be pointed out that the use of a transfer catalyst is an optional but not a distinguishing feature and therefore is the subject matter of claim 3. The relevant and distinguishing features of the invention have already been discussed above.

Specifically, the *Merbouh* (U.S. Patent No. 6,498,269) discloses in column 1, in lines 5 to 10 a method for the oxidation of aldehydes, hemiacetals, and primary alcohols. The

method finds particular utility in the production of monosaccharide aldaric acids and polyuronic acids.

More particularly, *Merbouh* from column 2, line 50 to column 3, line 17 discloses, in part, a method for the oxidation of substrates comprising treating an aqueous, basic solution of a substrate having an oxidizable functionality using an elemental halogen as terminal oxidant in the presence of an oxoammonium catalyst/halide co-catalyst system. In contrast to the prior art use of elemental halogen, preferably chlorine gas or elemental bromine, unexpectedly allows selective oxidation without significant degradation of the substrate. The substrate is preferably a monosaccharide, oligosaccharide, or polysaccharide, and the oxidizable functionality is preferably an aldehyde, hemiacetal, or a primary alcohol. An effective source of the oxoammonium catalyst is based on (TEMPO).

In a particularly preferred embodiment, a 5- or 6-carbon monosaccharide is oxidized to the corresponding aldaric acid, without substantial degradation of the backbone. The oxidized product may be isolated by filtration of the corresponding salts, or by acidification and extraction. The oxidation is highly selective for terminal groups, such that direct isolation of the product alkaline or alkaline metal salt from the reaction mixture yields analytically pure product.

This straightforward process in Merbouh produces highly desirable products in high yield and with high selectivity. The use of an inexpensive oxidant such as chlorine in an aqueous solvent allows for scaling up of the oxidation method based on monosaccharides to industrially relevant scales, thus providing significant advantages over other prior art methods.

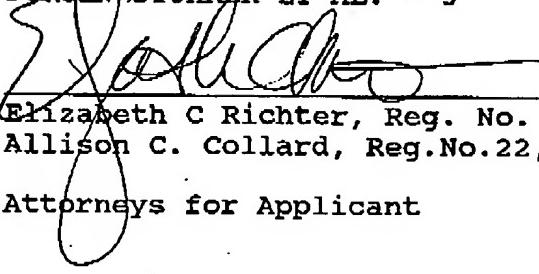
For all these reasons, *Merbouh* relates only to saturated alcohols, and not the claimed alkyne alcohols. Thus, this reference is nonanalogous prior art.

With respect to point 4 of the Office Action and the Terminal Disclaimer issue, it is respectfully pointed out that within the Office Action the most relevant differences between US 10/365,887 and the present invention are already summarized. There is no overlap in the claims because the present invention claims a process which is performed at "a pH of greater than 7", while US 10/365,887 refers to a process performed "at a pH less than 7".

In order to obtain good results using a pH of greater than 7 and to overcome the disadvantages already cited at Li et al., it has been surprisingly found that the claimed continuous process will overcome such problems.

In conclusion, the present invention and the pending remaining claims are believed to be patentable over the cited references. Early allowance of the claims is respectfully requested.

Respectfully submitted,
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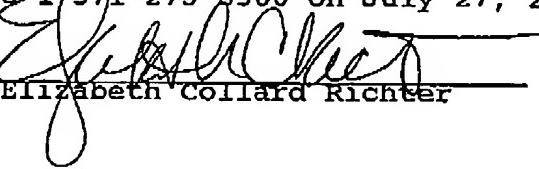
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I hereby certify that this correspondence is being sent by facsimile transmission to the U.S.P.T.O. to Patent Examiner C. Chang at Group No.1625, to 1-571-273-8300 on July 27, 2005.


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